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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,618	05/25/2005	Andreas Bergmann	2582.020	7130

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,618	BERGMANN, ANDREAS	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6,7 and 14-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,7 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/31/2009 has been entered.

2. Claims 1, 4, 6-7 and 14-17 are pending and under consideration as they read on a method for diagnosing sepsis comprising determining the amount of anti-asialo-GM1 antibodies (anti-AG_{Ml} antibodies) of the IgG and/or IgA type in blood, a blood fraction or secretion of a patient following a sepsis-risk event, wherein an elevated concentration of anti-asialo-GM1 antibodies in said blood compared to a healthy individual is indicative of sepsis.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 4, 6-7 and 14-17 *are* rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for**:** a method for determining an increased risk of sepsis in a

patient following a sepsis-risk event said method comprising determining the amount of anti-asialo-G_{M1} antibodies (anti-AG $_{M1}$ antibodies) of the IgG and/or IgA type in blood of a patient following the sepsis-risk event, wherein an elevated concentration of anti-asialo-G_{M1} antibodies in said blood compared to a healthy individual is indicative of an increased risk of sepsis; wherein said determining step is carried out with an assay type selected from a sandwich assay, a competitive assay and an agglutination assay; and wherein procalcitonin is simultaneously determined, the specification does not provide reasonable enablement for: **a method for making a diagnosis of sepsis**, said method comprising determining the amount of anti-asialo-G_{M1} antibodies (anti-AG $_{M1}$ antibodies) of the IgG and/or IgA type in blood, a blood fraction **or secretion** of a patient following a sepsis-risk event, **wherein an elevated concentration of anti-asialo-G_{M1} antibodies in said blood compared to a healthy individual is indicative of sepsis** of claim 1; wherein said determining step is carried out with an assay type selected from a sandwich assay, a competitive assay and an agglutination assay of claim 4; wherein **at least one further sepsis parameter** is simultaneously determined of claim 5; wherein the **at least one further parameter is procalcitonin** of claim 7; **a method for estimating the risk of a patient to develop sepsis following a sepsis risk-inducing event**, said method comprising: a) identifying a patient potentially at risk for sepsis following a sepsis risk- inducing event; and b) determining the level of anti-asialo-GMl (anti-AG M1) antibodies of the IgG and/or IgA type in a blood sample, blood fraction **or secretion** from said patient, **wherein an increased level of said antibodies in said sample indicates an increased risk that the patient will develop sepsis** of claim 14; **wherein said sepsis risk-inducing event is surgery, burn, or trauma** of claim 15; wherein said method is carried out using a ligand binding assay of the sandwich type,

or competitive type, or an agglutination assay of claim 16; and the method further comprising determining the level of procalcitonin, **wherein increased levels of procalcitonin and anti-AG $_{M1}$ antibodies of the IgG and/or IgA type when compared to normal individuals indicate an increased risk of the patient developing sepsis** of claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claims.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses in Figures 1-4 and on pages 25, line 20 to page 31, line 32 that serum from 20 sepsis patients were tested for the presence of antibodies which bind to A $G_{M1;}$ and 89 sepsis patients and 137 normal control patients were tested for the presence of antibodies which bind to G_{M1} and were 30 normal control patients were tested for the presence of antibodies which bind to A $G_{M1;}$ Immunoglobulin IgG and IgA subclasses were determined in the 20 sepsis

and 30 control patients that were tested for the presence of antibodies which bind to A G_{M1}. The specification discloses on page 31 that because sepsis patients had increased AG_{M1} antibodies of the IgA and IgG subclasses, without having increased AG_{M1} IgM antibodies, then the IgA and IgG antibodies were not formed as a result of the sepsis risk event. In other words, the IgA and IgG antibodies were already present in the patients and contributed to their sepsis or the antibodies were activated in the pre-sensitized immune system.

The specification does not adequately disclose a method for "diagnosis of sepsis" or "estimating the risk of a patient to develop sepsis." The specification establishes no causal link between sepsis and the antibodies. The previously cited art of art Badgwell et al. and Heremans et al. (PTO-892 mailed on 01/29/2008; References U and V) teach that sepsis is not causally linked to AG_{M1} IgG and IgA antibodies. Further, the method is not a method of "diagnosis" or "estimating the risk of a patient to develop sepsis " as anti-asialo GM1 antibody levels are increased over levels in healthy control patient in Graves Disease, Hashimoto's Thyroiditis, Acute Motor Neuropathy, Multiple Sclerosis, Systemic Lupus Erythematosus, Behcets's Disease and Polyradiculoneuropathy (PTO-892 mailed on 01/29/2008, Reference X on page 1 and U-X on page 2; In particular, whole documents). Because all of these patients have increased amounts of anti-asialo-GM1 antibodies (anti-AG_{M1} antibodies) and not sepsis, then anti-asialo-GM1 antibodies (anti-AG_{M1} antibodies) are not a diagnostic marker for sepsis or for estimating the risk of sepsis, even after a sepsis risk inducing event. Increased levels of anti-asialo-GM1 antibodies (anti-AG_{M1} antibodies) in a Graves Disease patient after thyroidectomy do not mean that the patient is undergoing sepsis. The same is true for any patient with the above conditions

who undergo the sepsis-risk events of surgery, burns or trauma. While the presence of increased anti-asialo-GM1 antibodies (anti-AG_{M1} antibodies) might increase a risk for sepsis, it does not diagnose or give information to estimate the risk of a patient to develop sepsis because increased anti-asialo-GM1 antibodies (anti-AG_{M1} antibodies) are associated with many disease states. Furthermore, there is no support in the specification for a method of predicting (estimating risk of a patient to develop) whether or not sepsis will happen in the future.

The specification has not adequately disclosed the genus of all "secretions" for use in the claimed invention. The specification provides inadequate support for the use of a secretion in the recited method. A skilled artisan would be required to perform undue experimentation to determine if these and other biological fluids can be used in the claimed invention.

In addition, the specification has not adequately disclosed a method for "diagnosis" or "estimating the risk of a patient to develop sepsis" comprising determining any "sepsis parameter" including procalcitonin for the same reasons as the specification has not adequately disclosed a method of "diagnosis" or "estimating the risk of a patient to develop sepsis" by measuring anti-asialo GM1 antibody levels. The art of Weglohner et al. (PTO-892; Reference U) teaches that procalcitonin is elevated in many conditions, including bacterial infection, parcreatitis, burns and polytrauma in addition to sepsis (In particular, 'Introduction'). As such, the art is unpredictable and a skilled artisan would be required to perform undue experimentation to practice the invention commensurate in scope with the claims.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments filed on 03/31/2009 have been fully considered, but are not found persuasive.

Applicant argues:

> "The Examiner has also taken the position that the disclosures of Badgwell et al. and Heremans et al. teach that sepsis is not causally linked to AG_{MI} IgG and IgA antibodies. Both Badgwell et al. and Heremans et al. implicate natural killer (NK) cells in the response to endotoxin-induced shock, using anti-AG_{M1} antibodies to deplete the subject animals of NK cells, with Heremans et al. observing that the depleted animals were rendered resistant to lethal reaction (page 1158, column 2, first paragraph under Discussion.) Neither reference, however, draws any conclusions regarding the role of anti-ganglioside antibodies in the development or diagnosis of sepsis.
>
> With respect to enablement, Applicant has identified a specific patient population to be tested for anti-AG M I antibodies of the IgG and/or IgA type, specifically patients who are at risk of developing sepsis following a sepsis risk- inducing event, for example, surgery, burn or other trauma. Accordingly, there is unlikely to be significant if any overlap with other disease states associated with increased levels of anti-AG MI antibodies. The significance of the claimed method is to provide early diagnosis of sepsis to ensure rapid intervention.
>
> Applicants urge that Figures 3 and 4 of the present application speak for themselves in establishing a positive correlation between anti-AG_{MI} antibody levels and sepsis: 100% of sepsis patients tested for anti-AG_{MI} antibodies of the IgA type had levels that were clearly elevated over control individuals (Figure 4). Furthermore, only one sepsis patient had levels similar to control individuals tested for anti-AGM~ antibodies of the IgG type; all others, that is, 95% of sepsis patients tested, had anti-AG_{MI} *antibody levels elevated over normal controls* (Figure 3). Thus, the skilled artisan would have no trouble distinguishing the sepsis group from the non-sepsis group; by extension, *elevated levels* of anti- AG_{MI} antibodies of the IgG or IgA subtype must indicate sepsis or a risk of sepsis, since elevated levels do not appear in non-sepsis individuals.
>
> With respect to measurement of "at least one further sepsis parameter", for example, procalcitonin, the use of procalcitonin as a biomarker for sepsis was well known in the art at the time the application was filed. (See discussion of procalcitonin in specification at pages 5 and 6 and US 5,639,617.) ."

It is the Examiner's position that as Applicant pointed out on page 29, lines 5-14 the specification does disclose that control patients were tested for the presence of antibodies which bind to AG_{M1}. However, it remains the Examiner's position that the instant recited methods are not enabled by the disclosure in the specification. The identification of a specific patient population does not limit the claims to an enabled method. Applicant's assertion that it "is unlikely to be significant if any overlap with other disease states associated with increased levels of anti-AG MI antibodies" is not persuasive. People undergoing trauma, surgery and burns are very likely to also have Graves Disease, Hashimoto's Thyroiditis, Acute Motor Neuropathy, Multiple Sclerosis, Systemic Lupus Erythematosus, Behcets's Disease or Polyradiculoneuropathy. Applicant's assertion that "elevated levels of anti- AG_{MI} antibodies of the IgG or IgA subtype must indicate sepsis or a risk of sepsis, since elevated levels do not appear in non-sepsis individuals" is simply not true. The art of record specifically teaches that Applicant has no basis for such a statement. It remains the Examiner's position that anti-asialo-GM1 antibodies (anti-AG_{MI} antibodies) are not a diagnostic marker for sepsis, with or without a sepsis risk event, nor do increased levels compared to a control give any information to estimate the risk of a patient to develop sepsis in the future. Therefore, the rejection is maintained.

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A

message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 11, 2009

Nora M. Rooney

Patent Examiner

Technology Center 1600

/Nora M Rooney/

Examiner, Art Unit 1644